European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination

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Background

In the current 28 Member States of the European Union (EU), approximately 34,000 new cases of cervical cancer and 13,000 deaths due to the disease occur annually [17]. Despite significant progress in Europe in recent decades in reducing the burden of cervical cancer, rates of death attributed to the disease are still high in many of the ‘new’ Member States that joined the EU after 2003: estimates of the annual age-standardized rates per 100,000 women in Hungary (63.9), the Slovak Republic (6.9), Poland (7.4), Latvia (8.2), Bulgaria (8.8) and Lithuania (9.8) are five to seven times higher, and in Romania (14.2), ten times higher than in Finland (1.4) and Malta (1.2), the EU Member States with the lowest rates in 2012. The age-standardized incidence rates of cervical cancer reveal a similar picture. The current 10-fold gradient in the mortality rates of cervical cancer among the EU Member States largely reflects the persistent absence, or inadequate implementation of cervical cancer screening programmes more than 10 years after organized, population-based screening programmes following European quality assurance guidelines were unanimously recommended by the Health Ministers of the EU [10].

Quality assurance aims to ensure that an endeavour leads to the outcome for which it is intended; this is particularly important for complex systems, such as screening programmes designed to lower the burden of cancer in the population [44]. The second edition of the European guidelines for quality assurance in cervical cancer screening [4,5] was published seven years ago. The continuing clear need to improve implementation of cervical cancer screening in the EU underlines the importance of re-emphasizing the European guidelines through the publication of the present supplements to the second edition. The supplements have been developed in a time of transition. Vaccination of girls and possibly also of boys in the future against the human papillomavirus (HPV) types that cause approximately 70% of cervical cancer has become an additional, complementary option of cervical cancer prevention, the main impact of which will emerge in a few decades when currently vaccinated girls are in their thirties and forties. In addition, cytology [1] is no longer the only test suitable for use in cervical cancer screening in the EU. The evidence presented in the first of the present supplements shows that primary testing for oncogenic HPV [3] fulfills the requirements for evidence-based screening tests laid down in the Council Recommendation [10], provided that cervical cancer screening programmes follow the recommendations for quality assurance published in the second edition [4,5] and the present supplements of the European guidelines [2,11,34].

Of particular importance is the recent evidence from the second round of European randomized controlled trials showing a more pronounced effect of cervical screening using HPV primary testing compared to cytology-based screening [32,6]. Given the evidence for improved efficacy of HPV primary screening that is explained in the first supplement, decision-makers, advocates, professionals, and women in the EU are increasingly confronted with the question of whether or not, and if so, how these new developments should be integrated into more successful approaches to control cervical cancer in Europe, both for the individual women affected and for the population as a whole. By focusing on the core topics of primary HPV testing in the first supplement [34], organization of HPV-based and cytology-based screening programmes in the second supplement [2], and implementation of HPV vaccination programmes in the third supplement [11], the joint publication of these supplements aims to provide appropriate answers to these important questions and to lay the foundation for further development of the comprehensive European guidelines in the coming years.

Publication format

The supplements are presented in a joint volume including 62 main recommendations and conclusions for which the strength of the evidence and the respective recommendations is graded according to a defined format. These recommendations are presented at the beginning of each supplement and their annotation indicates the places in the subsequent text where the evidence and the rationale pertaining to each recommendation are explained, including cross-references to other supplements and recommendations. This enables the reader to readily review the key content of the supplements and to identify places in the volume likely to be of interest for further reading. In addition, some statements of advisory character are considered to be good practice but not sufficiently important to warrant formal grading are provided in each supplement.

Methodology

To develop the evidence-based recommendations, the approach used for the European guidelines for quality assurance in colorectal cancer screening and diagnosis [27] was adopted and modified slightly to take into account the different subject matter and time period of the present project. A multidisciplinary group of authors and editors experienced in quality assurance in cervical cancer screening, programme implementation and guideline development collaborated with a ‘literature group’ consisting of epidemiologists with special expertise in the field of cervical cancer screening and in systematic literature review. Experts in HPV vaccination were also

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Suitability of HPV primary testing for use in cervical cancer screening programmes

1.1 Primary testing for oncogenic HPV\(^+\) can be used in an organized, population-based programme for cervical cancer screening (I-A). Primary testing for oncogenic HPV outside an organized population-based programme is not recommended (see also Suppl. 2, Rec. 2.1) (VI-C)\(^{I-A}\). \(^{1.2.2}\)

### Avoidance of co-testing (HPV and cytology primary testing) at any given age

1.2 Only one primary test (either cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3–1.7) (II-A)\(^{I-D}\). \(^{1.2.3}\)

### Age at which to start HPV primary testing in cervical cancer screening programmes

1.3 Routine HPV primary screening can begin at age 35 years or above (see also Rec. 1.1) (I-B)\(^{I-C}\). \(^{1.3.2}\)

1.4 Routine HPV primary screening should not begin under age 30 years (I-E)\(^{VI-A}\). \(^{1.3.3}\)

1.5 The available evidence is insufficient to recommend for or against beginning routine HPV primary screening in the age range 30–34 years (IV-C)\(^{I-C}\). \(^{1.3.4}\)

### Age at which to stop HPV primary testing in cervical cancer screening programmes

1.6 In the absence of sufficient evidence on the optimal age at which to stop screening, HPV primary screening could stop at the upper age limit recommended for cytology primary screening (60 or 65 years), provided a woman has had a recent negative test (VI-B)\(^{I-A}\). \(^{1.3.5}\)

### Cervical screening using cytology primary testing outside the age range of HPV primary testing

1.7 Cervical screening based on cytology primary testing conducted outside the age range of HPV primary testing should follow the guidance provided for cytology-based screening in the second edition of the European guidelines for quality assurance in cervical cancer screening, and in Supplement 2 (see also Rec. 1.9, 1.10, 1.22 and 1.34) (VI-B)\(^{I-A}\). \(^{1.3.6}\)

### Screening interval after a negative HPV primary test

1.8 The screening interval for women with a negative HPV primary test result should be at least 5 years (I-A) and may be extended up to 10 years depending on the age and screening history (II-C)\(^{I-A}\). \(^{1.3.7}\)

#### Management of women without an adequate HPV primary test result

1.9 Some women attending cervical cancer screening may prefer not to be tested for HPV. If a woman declines HPV primary testing, cytology can be performed (see also Rec. 1.7) (VI-C)\(^{I-A}\). \(^{1.3.8}\)

1.10 Non-attenders and women with a technically inadequate HPV test result should be invited to have a new sample taken (VI-A), alternatively cytology testing without additional sample taking may be performed if technically feasible and preferred by the woman (see also Suppl. 2, Rec. 2.9–2.11) (VI-B)\(^{I-A}\). \(^{1.3.9}\)

#### Management of women after a positive HPV primary test

1.11 Cervical screening programmes using HPV primary testing must adopt specific policies on triage, referral and repeat testing of women with positive primary test results, taking into account the guidance in Rec. 1.12–1.13. The policies must include guidance on when women with positive HPV test results should be invited to return to routine screening (VI-A)\(^{I-A}\). \(^{1.3.10}\)

1.12 Screening programmes should carefully monitor management of HPV-positive women. Monitoring should include compliance of individual women with repeat follow-up of positive primary test results, as well as results of triage, referral, colposcopies, biopsies, and treatment of precancers (VI-A)\(^{I-A}\). \(^{1.3.11}\)

1.13 Triage, referral and repeat testing policies (see Rec. 1.11) should be regularly reviewed and, if necessary, revised taking into account the results of monitoring (see Rec. 1.12) and the available evidence (VI-A)\(^{I-A}\). \(^{1.3.12}\)

#### Secondary testing

- **Cytology triage**

1.14 Women testing positive for oncogenic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) (I-A)\(^{I-A}\). \(^{1.3.13}\) The cytology test should preferably use the specimen collected during the HPV screening visit (VI-A)\(^{I-A}\). \(^{1.3.14}\)

1.15 Direct referral to colposcopy of all HPV-positive women is not recommended (I-D)\(^{I-A}\). \(^{1.3.15}\)

1.16 Depending on the result of cytology triage, HPV-positive women should be referred to repeat testing, or to colposcopy (see Rec. 1.18–1.21) (I-A)\(^{I-A}\). \(^{1.3.16}\)

1.17 Quality assurance of laboratories and professional practice in the provision of cytology, colposcopy and histopathology services used in cytology triage in HPV primary screening should comply with the recommendations in Chap. 3–6 of the European Guidelines second edition (see also Rec. 1.35) (VI-B)\(^{II-C}\). \(^{1.3.17}\)

- **Referral of women with pre-invasive or more severe cytology at triage**

1.18 Women with ASC-H (atypical squamous cells, high-grade squamous lesion cannot be excluded), HSIL (high grade squamous intraepithelial lesion), AIS (adenocarcinoma in situ) or a more severe finding at cytology triage should be referred to colposcopy without further observation or testing (II-B)\(^{I-C}\). \(^{1.3.18}\)

1.19 **Referral of women with minor cytological abnormalities at initial triage**

1.20 Women with ASC-US (atypical squamous cells of undetermined significance), AGC (atypical glandular cells), or LSIL (low grade squamous intraepithelial lesion) at triage after an initial HPV primary test in a screening episode may be followed up by retesting, preferably after 6–12 months, or referred directly to colposcopy (see Rec. 1.22–1.33) (VI-C)\(^{I-A}\). \(^{1.3.19}\)

1.21 Direct referral to colposcopy of women with negative cytology at triage is not recommended (I-D)\(^{I-A}\). \(^{1.3.20}\)

#### Management of women at repeat testing

1.22 The prevalence of HPV and the quality and organization of cytology screening affect the efficiency, effectiveness and appropriateness of management of women at repeat testing. These factors should be taken into account in the regular review of management protocols for repeat testing (see also rec. 1.113) (VI-C)\(^{I-A}\). \(^{1.3.21}\)

- **Type and interval of repeat testing**

1.23 Cytology repeat testing after at least 6–12 months is an acceptable alternative to HPV repeat testing (see also Chap. 6, Sect. 6.3.1 in European Guidelines, second edition) (II-B)\(^{I-C}\). \(^{1.3.22}\)

1.24 Women who were HPV-positive and cytology normal (negative for epithelial abnormality) in primary screening may be managed by HPV retesting with or without cytology triage, and after an interval of preferably at least 12 months (II-B)\(^{I-C}\). \(^{1.3.23}\)

- **Protocols using HPV testing with cytology triage in repeat testing**

1.25 Women who were referred to colposcopy if cytology triage of a positive repeat HPV test yields ASC-US (VI-B) or more severe cytology (VI-A)\(^{I-A}\). \(^{1.3.24}\)

1.26 Women who have negative cytology triage (negative for epithelial abnormality) of a positive (repeat HPV test) may be managed by one of the following options (see also Rec. 1.113–1.113) (VI-B)\(^{II-C}\). \(^{1.3.25}\)

- Referral to second repeat testing after at least 12 months
- Referral to colposcopy
- Return to routine screening

1.27 Women who have a negative repeat HPV test should return to routine screening (II-B)\(^{I-A}\). Cytology triage is not needed for these women (II-B)\(^{I-A}\). \(^{1.3.26}\)

- **Protocols using cytology testing alone in repeat testing**

1.28 Women with ASC-US or more severe cytology at repeat testing should be referred to colposcopy (VI-B)\(^{I-A}\). \(^{1.3.27}\)

1.29 Women with normal cytology at repeat testing should return to routine screening (II-B)\(^{I-A}\). \(^{1.3.28}\)

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**Table 1**

Screening for cervical cancer with primary testing for human papillomavirus\(^+\). Recommendations and conclusions. Supplement 1\(^+\).
Suitability of HPV primary testing for use in cervical cancer screening programmes

- Protocols using HPV testing alone in repeat testing
  - Women who have a negative repeat HPV test should return to routine screening (B-A). (Rec. 1.3)
  - Women who have a positive repeat HPV test should be referred to colposcopy (B-C). (Rec. 1.3)

Self-sampling in screening programmes using HPV primary testing

The clinical accuracy of HPV primary testing on self-collected samples taken for cervical screening is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec. 2.8–2.13). (Rec. 1.33)

Selection of HPV tests suitable for primary cervical cancer screening

- Cervical cancer screening programmes should adopt an HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV infections (VI-A). (Rec. 1.34)

Implementation of HPV primary testing in cervical cancer screening programmes

- HPV primary screening programmes should follow the guidance in the European Guidelines, that is relevant to any cervical screening programme irrespective of the method of primary testing used. The relevant guidance includes the recommendations on programme organization, planning, monitoring and evaluation (see current Suppl. 2, and second edition, Chap. 2); communication; and quality assurance of the entire screening process including sampling, histopathologic interpretation and classification of cervical tissue; and management of detected lesions (see second edition, Appendix 1 and Chap. 3–6) (VI-A). (Rec. 1.35)

- Like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards. The laboratory should perform a minimum of 10,000 tests per year (see also Rec. 1.34) (VI-A). (Rec. 1.36)

- Any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in this supplement can be organized (VI-B). (Rec. 1.37)

- Health economic factors to consider in planning and subsequent steps in programme implementation include the prevalence of HPV infections; the burden of repeat testing, colposcopies, and CIN treatments resulting from HPV testing; and the quality and impact of existing cytology screening programmes.

- Assessments should be conducted to determine the optimal target age groups and screening intervals based on the chosen test and management protocols.

- The feasibility and sustainability of the programme should be assured through adequate resourcing and coordination, including coordinated planning, feasibility pilot studies, and quality-controlled rollout across a country or region (see Suppl. 2 and Annex 1).

Grading of recommendations and supporting evidence

For the level of evidence:

I. Consistent multiple randomised controlled trials (RCTs) of adequate sample size, or systematic reviews (SRs) of RCTs, taking into account heterogeneity

II. One RCT of adequate sample size, or one or more RCTs with small sample size

III. Prospective cohort studies or SRs of cohort studies; for diagnostic accuracy questions, cross-sectional studies with verification by a reference standard

IV. Retrospective case-control studies or SRs of case-control studies, trend analyses

V. Case series; before/after studies without control group, cross-sectional surveys

VI. Expert opinion

For the strength of the respective recommendation:

A. Intervention strongly recommended for all patients or targeted individuals

B. Intervention recommended

C. Intervention to be considered but with uncertainty about its impact

D. Intervention not recommended

E. Intervention strongly not recommended

Screening for cervical cancer with primary testing for human papillomavirus

The first of the present supplements [34] aims to inform European policy makers and public health specialists, and any other interested parties about the critical issues that should be

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considered in weighing the potential benefit and harm of cervical screening programmes based on HPV primary testing. It includes 36 graded recommendations dealing with the suitability of HPV primary testing for use in cervical cancer screening. Key messages and topics covered in the supplement include the lack of appropriate benefits from co-testing, and the appropriate target age group and interval for HPV primary testing. Management protocols for women with positive or technically inadequate HPV primary tests, the clinical accuracy of HPV testing using self-collected samples, and the selection of tests suitable for primary screening are also covered; and other policies and professional and scientific standards, such as consideration of health economic issues, are indicated that should be adhered to in the design and implementation of quality-assured cervical cancer screening programmes based on HPV primary testing. It is not the intention of the authors and editors to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. The supplement therefore focuses on the use of primary testing for HPV DNA in cervical cancer screening with cytology triage in the EU. As far as possible the authors and editors have attempted to achieve an equitable balance that is applicable across a wide spectrum of cultural and economic healthcare settings in the EU. As with any standards and recommendations, these should be continuously reviewed in the light of future experience.

The scientific justification for the recommendations in the first supplement is provided by over 110 publications cited in the text, including published cross-sectional and longitudinal data from eight randomized controlled trials conducted in Canada, Finland, India, Italy, Sweden, The Netherlands and the United Kingdom (18.12.20-24.26,28,29,32,33,35-40). It should be noted that the efficacy of HPV primary testing in cervical cancer screening has been demonstrated in studies using clinician-based samples. The authors and editors emphasize that currently the clinical accuracy of HPV primary testing on self-collected samples is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (Rec. 1.32 in Suppl. 1 [34], see also Table 1). Policy makers and professionals must be aware, however, that HPV testing on self-taken samples is less accurate than clinician-based samples. For this reason, self-sampling is not recommended for all women invited to screening (see Sect. 1.7 in [34] and Sect. 2.4.4 and Rec. 2.8-2.13 in Suppl. 2 [2], see also Table 2).

The authors and editors also emphasize that despite the convincing evidence for more efficacious screening using HPV primary testing,
Organization of cytology-based or HPV-based cervical cancer screening

The second supplement [2] addresses the persisting gap in the EU between knowledge of the potential of population-based cervical screening to reduce the burden of the disease in the population, on the one hand, and the extent to which this knowledge has been translated into effective national programmes to control cervical cancer, on the other hand. As pointed out in the Council Recommendation on cervical cancer screening while minimizing the risks (see Rec. 1.11 in [34], see also Table 1).

While most of the recommendations in the first supplement focus on the opportunities and the challenges of HPV primary screening that set it apart from cytology-based screening: decision-makers, programme managers and professionals should also be aware of the guidance in the previously published volume of the second Guidelines edition [4,5] that is relevant to any cervical screening programme irrespective of the method of primary testing used (see Rec. 1.34). Of prime importance in this regard are also the recommendations on programme organization, planning, monitoring and evaluation in the second supplement. The authors and editors also emphasize the importance of using reliable, validated HPV tests (see Rec. 1.33) in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards (see Rec. 1.35). In addition, any decision to implement HPV primary testing in cervical cancer screening should take into account health economic factors, and whether correct use of the test as specified in the instructions of the manufacturer and in accordance with the recommendations in the supplement can be organized (see Rec. 1.36). The authors and editors also point out that sustainability is crucial to the success of any cervical screening programme, and in the first supplement they underline the importance of the respective recommendations in Supplement 2 and in Annex 1 of the Supplements volume.

Implementation of vaccination against human papillomavirus in Europe

The third of the present supplements [11] summarizes the evidence base for HPV vaccination using the currently licensed bivalent and quadrivalent vaccines in the EU. Over 90 publications are cited and nine graded recommendations are provided to promote effective implementation of this tool for cervical cancer control in the EU. Clinical trials have shown the current prophylactic HPV vaccines to be safe and highly effective against persistent vaccine-related HPV infections and anogenital precancerous lesions among women who were not infected by these types at the time of vaccination [13,46,48]; see also [15,16]. The use of HPV vaccines in pre-adolescent girls and young women for the primary prevention of cervical cancer and some other HPV-related diseases has been endorsed by the European Medicines Agency (EMA) in 2006 (quadrivalent HPV 6/11/16/18 vaccine) and 2007 (bivalent HPV 16/18 vaccine), and in a position paper by the World Health Organization (WHO) in 2009 and 2014 [47,49]. Since then, 21 of the 28 Member States of the European Union plus Norway and Iceland have introduced national HPV vaccination programmes. Recently, WHO updated its HPV vaccines position paper to recommend a two-dose regimen with increased flexibility in the interval between doses [49]. EMA has also granted marketing authorizations for bivalent and quadrivalent vaccines in the EU for a two-

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Individual vaccination records should be retained, to permit linkage of data by year of birth and number of administered doses. In addition, targeted while being pregnant. An important measure in process-special groups such as women who have been inadvertently vaccinated while being pregnant. An important measure in process-special groups such as women who have been inadvertently vaccinated while being pregnant.

Events like autoimmune diseases, or possible adverse effects in vaccinated subjects. Moreover, mathematical modelling studies suggest that cooperative vaccination programmes can accelerate the impact of the vaccination programmes. However, long-term monitoring of end-point indicators is essential to assure that programmes attain their expected impact. This will require careful assessment of changes in the epidemiology of severe precancerous lesions and cancers over decades through linkage between screening and cancer registries irrespective of early indicator studies.

As of early 2014, seven EU countries had not yet initiated HPV vaccination campaigns, all of them new Member States (Estonia, Hungary, Lithuania, Poland, Slovakia, Cyprus and Croatia). HPV vaccination is perceived as being too expensive by many new Member States, but vaccine prices for vaccination campaigns have decreased considerably in recent years, and modelling studies have shown that cost-effectiveness of HPV vaccination tends to be largest in countries with the highest cervical cancer burden, as is the case in most of these countries.

In most of the EU Member States with HPV vaccination campaigns, the vaccine is offered free of charge, predominantly through organized, population-based programmes distributing the vaccine at schools or public health centres. The success in terms of coverage of the target groups has been highly variable, ranging from 30% to 80% and over.

At the lower end of the range, in France and Luxemburg, the vaccination status should be known to screening and vaccination registries for women reaching the target screening age (VI-A, Sect. 3.8).

Coverage target for HPV vaccination programmes

HPV vaccination programmes should aim for a minimum coverage of 70% and preferably 80% (VI-A, Sect. 3.6).

HPV screening and HPV vaccination

Vaccination status should be known to screening and vaccination registries for women reaching the target screening age (VI-A, Sect. 3.8).

Planning, piloting, and modifying HPV vaccination programmes

Planning and modification of vaccination programmes and policies should take into account local conditions, including vaccine and vaccination costs and resources required in monitoring, provision of information, and communication. Pilot studies are recommended to assess how to improve coverage and public awareness (VI-A, Sect. 3.5).

Procurement

Decision-makers should be aware of the wide range of prices for HPV vaccines in the EU and the potential to reduce the overall costs of HPV vaccination programmes by negotiating vaccine prices that are comparable to the low prices obtained in some EU Member States (VI-A, Sect. 3.5).

The primary target group for routine vaccination is girls at an age before the onset of sexual activity, usually between 10 and 13 years (VI-A, Sect. 3.2).

Monitoring and evaluation of HPV vaccination programmes

Organized, population-based HPV vaccination programmes should have systematic register-based monitoring of coverage and safety. Long-term evaluation of vaccine safety and effectiveness is recommended in all countries. Appropriate legal frameworks must be developed, taking funding and organizational resources into account (VI-A, Sect. 3.3).

Coordination between vaccine evaluation and cancer control programmes is recommended. It will be critical to assess the impact of the vaccine and its synergies with screening and health education (VI-A, Sect. 3.5).

The minimum set of information for monitoring HPV vaccination should include data on vaccine coverage, monitoring of adverse events following immunization and, if possible, a sentinel surveillance of impact on precancerous lesions (VI-A, Sect. 3.3).

Age at primary vaccination, age at catch-up vaccination, number of doses by single year of age and time between doses, and duration of follow-up since offering vaccination to girls as well as to women in the catch-up strategy should be included in the definitions and performance parameters (VI-A, Sect. 3.3).

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HPV vaccination programmes should aim for a minimum coverage of 70% and preferably > 80% (VI-A, Sect. 3.6).

The reported 3-dose coverage of primary vaccination in a population-based vaccination programme should reach 70% within the first 12 months (III-A). The same coverage target applies for programmes using a 2-dose schedule (VI-A, Sect. 3.6).

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Vaccination status should be known to screening and vaccination registries for women reaching the target screening age (VI-A, Sect. 3.8).

Planning and research on synergies between HPV vaccination and HPV screening is recommended to improve the effectiveness and cost-effectiveness of prevention of HPV-related disease (VI-A, Sect. 3.9).

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programs rely on opportunistic vaccination. The highest rates of
80% and above are in countries or regions with population-based
vaccination programmes (Denmark, Malta, Portugal, Sweden and the
UK and Flemish community in Belgium). Most of the countries choose
routine target groups that include ages in the range 11–13 years.
Organized school-based programmes usually provide the best cover-
age and more equitable access to HPV vaccines, followed by organized
programmes through health-care centres and through general practi-
tioners. Opportunistic programmes usually achieve low or ill-defined
levels of coverage. Vaccination campaigns targeting adolescents pose
specific challenges, compared to those targeting younger children
aged 10–13 years.

Given the current variation in HPV vaccination coverage in the EU,
the importance of an organized, population-based approach to vaccine
delivery and the need for adaptation of existing vaccine delivery
infrastructure to the special requirements of HPV vaccination are
common to all EU countries (see Rec. 3.1 in Suppl. 3[11], see also
infrastructure to the special requirements of HPV vaccination are
Table 3). Higher vaccination coverage is a reasonable goal in many EU
Member States. HPV vaccination programmes should aim at a mini-
mum coverage of 70% and preferably > 80% (see Rec. 3.6). Effective
monitoring and evaluation will be key to improving the coverage and
effectiveness of vaccination programmes across the EU. Organized,
population-based HPV vaccination programmes should have systema-
tic register-based monitoring of coverage and safety. Long-term
evaluation of vaccine safety and effectiveness is recommended in all
countries. Appropriate legal frameworks must be developed, taking
funding and organizational resources into account (see Rec. 3.3). Every
effort should be made to record individual vaccination status to ensure
that it will be known for future cohorts reaching the target age for
screening (see Rec. 3.8).

Discussion and conclusions

In an evidence-based process, supplements have been devel-
oped that expand the current second edition of the European
guidelines for quality assurance in cervical cancer screening [4,5]
to cover topics essential to successful implementation of
population-based programmes for HPV primary screening and
vaccination. In addition to a large package of recommendations
graded according to the strength of the recommendations and the
supporting evidence, numerous recommendations considered to
be good practice by the authors and editors but not of sufficient
importance to warrant formal grading are provided in the 200-
page Supplements volume that will be published by the European
Commission. Neither the Supplements volume nor the previously
published volume of the second Guidelines edition should be
regarded as a text book or in any way a substitute for practical
clinical training and experience, but together they provide impor-
tant European reference documents that decision makers in EU
Member States and other countries should consult to determine
whether current policies and programmes for cervical cancer
prevention and control can be improved before a new and fully
revised third edition of the European guidelines becomes
available.

The need for further improvement in cervical cancer preven-
tion and control in Europe, particularly in many of the newer EU
Member States is the rationale for focusing the present supple-
ments on topics relevant to HPV primary screening and vaccina-
tion. The completion of the supplements by a multidisciplinary
group of experts in cervical screening, HPV vaccination and quality
assurance and their publication by the European Commission has
the potential to become a watershed in improvement of cervical
cancer prevention and control in Europe. Based on robust evidence
the editors of the supplements explain that cytology primary
testing is no longer the only method for population-based cervical
cancer screening that fulfills the requirements of the Council
Recommendation on Cancer Screening of 2 December 2003. HPV
primary testing is also an appropriate, evidence-based screening
method, provided the recommendations in the supplements are
followed in programme implementation.

Recognition of the conformity of cervical cancer screening based
on HPV primary testing with the Council Recommendation on Cancer
Screening is of prime importance because the first report on cancer
screening in the EU documented considerable interest in the EU
members states in following through on the Council Recommenda-
tion by establishing and improving cancer screening programmes
in accordance with European Guidelines for quality assurance [9,42].
Raising awareness for the supplements through publication of the
present summary should encourage responsible authorities and
programme managers to review current policies to determine
whether further improvement in cervical cancer prevention and
control may be achieved through modification of existing screening
programmes or implementation of new, HPV-based programmes
where cervical screening programmes are lacking; and through
optimized implementation of HPV vaccination.

The choice of content of the present summary is to some extent
arbitrary and cannot in any way be regarded as an alternative to
the requirement for reading each supplement as a whole and
within the context of the complete second edition of the European
quality assurance guidelines [4]. This will be possible when the full
Supplements volume is available. It should be kept in mind
however, that despite encouraging progress, the availability of
the extensive supplements will not provide answers to all of the
questions that are relevant to future improvement in cervical
cancer prevention and control in Europe. Additional points, such
as the potential role of methods other than cytology in triaging
women with positive HPV test results and evaluation of new
primary tests and vaccines require further attention.

It has recently been pointed out that the variation in Europe in the
implementation of cancer screening offers a unique opportunity
to learn from best practices in collaboration between cancer registries
and screening programmes [3] and in quality assurance [14]. In order
to accelerate improvements in cancer control, cancer registries should
take co-responsibility with screening and vaccination programmes
and registries in promoting continuous improvement of primary and
secondary cancer prevention in Europe. Additional sustainable invest-
ments are vital to further development of infrastructures and activities
for quality assurance, including organization training, evaluation and
monitoring in the national settings and also at the pan-European level.
This is an important point that is also emphasized in Annex 1 [43] of
the Supplements volume and that not only applies to cervical cancer
screening but also HPV vaccination [3,14].

Disclaimer

The views expressed in this document are those of the authors.
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any person acting alone or on behalf of others can be held
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this document.

The authors of the present manuscript are the members of the
editorial board of the current supplements to the second edition of
the European guidelines for quality assurance in cervical cancer
screening. J. Dillner served on the editorial board only for issues
related to screening, not vaccination.

Competing interests

J. Dillner has received research grants to his university with
significant funding from Merck/S PMID, a manufacturer of HPV

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vaccines, for monitoring studies on HPV vaccines. He declares no personal remuneration.

L. Dillner is the spouse of J. Dillner who has reported the competing interest listed above.

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